PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GARDNER, Rebecca
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL
ROYAUME-UNI

Date of mailing (day/month/year)
28 January 2002 (28.01.02)

Applicant's or agent's file reference
9.69402/001

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02551

International filing date (day/month/year)
03 July 2000 (03.07.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
CORTENDO AB
Södra Förstadsgatan 2
S-211 43 Malmö
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
CORTENDO AB
Gruvgatan 6
S-42130 Västra Frölunda
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Sean Taylor
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION T _ATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GARDNER, Rebecca
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL
ROYAUME-UNI

Date of mailing (day/month/year) 05 December 2001 (05.12.01)	
Applicant's or agent's file reference 9.69402/001	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/02551	**International filing date** (day/month/year) 03 July 2000 (03.07.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
GARDNER, Rebecca Frank B. Dehn & Co. 179 Queen Victoria Street London EC4V 4EL United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The applicant identified in Box 1 has been removed from the records, since she assigned all her rights to her co-applicant, CORTENDO AB.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 March 2001 (02.03.01)	
International application No. PCT/GB00/02551	**Applicant's or agent's file reference** 9.69402/001
International filing date (day/month/year) 03 July 2000 (03.07.00)	**Priority date** (day/month/year) 02 July 1999 (02.07.99)
Applicant MARIN, Per et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 February 2001 (02.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Dominique DELMAS

Telephone No.: (41-22) 338.83.38

10/019613

PATENT COOPERATION TREATY

PCT

REC'D 09 OCT 2001

WIPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9.32.69402/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02551	03/07/2000	02/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant CORTENDO AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/02/2001	04.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02551

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11 in respect of industrial applicability.

because:

☒ the said international application, or the said claims Nos. in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3, 6-10 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 3-5, 8-9, 12
	No:	Claims 1-2, 6-7, 10-11
Inventive step (IS)	Yes:	Claims 8-9
	No:	Claims 1-7, 10-12
Industrial applicability (IA)	Yes:	Claims 1-10, 12

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Claims 1-3 and 6-10 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefor are the following:
Claims 1-3 and 6-10 refer to the use of cortisol antagonists for treating heart failure. No further technical characteristics are given for the cortisol antagonists. Consequently, the an opinion will be formulated for those parts of the application which have actually been searched, namely the use of the cortisol antagonists explicitly disclosed at page 6, lines 8-30 in the description, as well as the compounds of claims 4-5.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
Reference is made to the following documents:
D1: US-A-4603141
D2: Derwent abstract, AN: 90080584 (& Kardiologiia, Sep. 1989, 29(9), 81-3)

1. Document D1 discloses (see the whole document) the use of clonidine for treating congestive heart failure and increase the exercise tolerance of such an individual. Clonidine is expicitly mentioned in the application at page 6 as one of the cortisole antagonists for use in the present invention. The subject matter of claims 1-2, 6-7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

2. Document D2 discloses (see abstract) that synthetic opioids, such as synthetic enkephalins, possess cardioprotective effects and can be used to reverse stress-induced damage of the myocardium. Enkephalins are amongst the substances

disclosed for use in the present invention. The subject matter of claims 1-2, 7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

3. An objection of lack of inventive step (Art. 33(3) PCT) is also raised against the subject matter of claims 3-5 of the present application for the following reasons. Document D1, which is considered to represent the closest prior art, discloses the use of clonidine, an antihypertensive known to act as cortisol antagonist, for the treatment of congestive heart failure. The subject matter of calims 3-5 differs from that of D1 in that an inhibitor of cortisol synthesis, namely ketoconazole, is used instead. Substitution of a known cortisol antagonist for another known one for treating the same disease, in this case heart failure, can only be considered as inventive if it leads to unexpected results.

4. The above inventive step objection (Art. 33(3) PCT) applies also to the subject matter of claim 12 which relates to combination compositions of a cortisol antagonist and a second drug for treating heart failure. As in above such combination can only be considered as inventive if it leads to unexpected results.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0018424	06.04.00	27.09.99	25.09.98

Document WO-A-0018424 discloses (see claims 1, 4-8) pharmaceutical compositions containing substances having oxytocin activity for improving cell regeneration after a heart attack, and is therefore prejudicial to the novelty of claims 1-2, 7 and 10-11 of the present application. Nevertheless, the validity of filng and priority dates has not been checked.

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0024402	04.05.00	27.10.98	

Document WO-A-0024402 discloses (see claims 1, 2, 5, 8-9) pharmaceutical

compositions containing antifungal agents, ketoconazole being explicitly mentioned, for treating tissue scleroses in mammals. Tissue scleroses resulting from myocardial infarction are explicitly mentioned. Document WO-A-0024402 is therefore prejudicial for the novelty of claims 1-4, 7, 9-11 of the present application.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII

Certain observations on the international application

In claim 12 the term "second drug" is unclear. It should be defined according to the description, page 13, lines 10-11 as "second drug effective in the treatment of heart failure".

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9.32.69402/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02551	03/07/2000	02/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant CORTENDO AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/02/2001	04.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02551

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11 in respect of industrial applicability.

because:

☒ the said international application, or the said claims Nos. in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3, 6-10 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 3-5, 8-9, 12
	No:	Claims 1-2, 6-7, 10-11
Inventive step (IS)	Yes:	Claims 8-9
	No:	Claims 1-7, 10-12
Industrial applicability (IA)	Yes:	Claims 1-10, 12

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Claims 1-3 and 6-10 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefor are the following:
Claims 1-3 and 6-10 refer to the use of cortisol antagonists for treating heart failure. No further technical characteristics are given for the cortisol antagonists. Consequently, the an opinion will be formulated for those parts of the application which have actually been searched, namely the use of the cortisol antagonists explicitly disclosed at page 6, lines 8-30 in the description, as well as the compounds of claims 4-5.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
Reference is made to the following documents:
D1: US-A-4603141
D2: Derwent abstract, AN: 90080584 (& Kardiologiia, Sep. 1989, 29(9), 81-3)

1. Document D1 discloses (see the whole document) the use of clonidine for treating congestive heart failure and increase the exercise tolerance of such an individual. Clonidine is expicitly mentioned in the application at page 6 as one of the cortisole antagonists for use in the present invention. The subject matter of claims 1-2, 6-7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

2. Document D2 discloses (see abstract) that synthetic opioids, such as synthetic enkephalins, possess cardioprotective effects and can be used to reverse stress-induced damage of the myocardium. Enkephalins are amongst the substances

disclosed for use in the present invention. The subject matter of claims 1-2, 7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

3. An objection of lack of inventive step (Art. 33(3) PCT) is also raised against the subject matter of claims 3-5 of the present application for the following reasons. Document D1, which is considered to represent the closest prior art, discloses the use of clonidine, an antihypertensive known to act as cortisol antagonist, for the treatment of congestive heart failure. The subject matter of calims 3-5 differs from that of D1 in that an inhibitor of cortisol synthesis, namely ketoconazole, is used instead. Substitution of a known cortisol antagonist for another known one for treating the same disease, in this case heart failure, can only be considered as inventive if it leads to unexpected results.

4. The above inventive step objection (Art. 33(3) PCT) applies also to the subject matter of claim 12 which relates to combination compositions of a cortisol antagonist and a second drug for treating heart failure. As in above such combination can only be considered as inventive if it leads to unexpected results.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0018424	06.04.00	27.09.99	25.09.98

Document WO-A-0018424 discloses (see claims 1, 4-8) pharmaceutical compositions containing substances having oxytocin activity for improving cell regeneration after a heart attack, and is therefore prejudicial to the novelty of claims 1-2, 7 and 10-11 of the present application. Nevertheless, the validity of filng and priority dates has not been checked.

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0024402	04.05.00	27.10.98	

Document WO-A-0024402 discloses (see claims 1, 2, 5, 8-9) pharmaceutical

compositions containing antifungal agents, ketoconazole being explicitly mentioned, for treating tissue scleroses in mammals. Tissue scleroses resulting from myocardial infarction are explicitly mentioned. Document WO-A-0024402 is therefore prejudicial for the novelty of claims 1-4, 7, 9-11 of the present application.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII

Certain observations on the international application

In claim 12 the term "second drug" is unclear. It should be defined according to the description, page 13, lines 10-11 as "second drug effective in the treatment of heart failure".

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/01971 A1

(51) International Patent Classification[7]: A61K 31/00, A61P 9/04

(21) International Application Number: PCT/GB00/02551

(22) International Filing Date: 3 July 2000 (03.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915625.9 2 July 1999 (02.07.1999) GB

(71) Applicant *(for all designated States except US)*: **CORTENDO AB** [SE/SE]; Södra Förstadsgatan 2, S-211 43 Malmö (SE).

(71) Applicant *(for GB only)*: **GARDNER, Rebecca** [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MARIN, Per** [SE/SE]; Nolebrunnsgatan 25, S-426 77 Västra Frölunda (SE). **SORENSEN, Sten** [SE/SE]; Cortendo AB, Södra Förstadsgatan 2, S-211 43 Malmö (SE).

(74) Agents: **GARDNER, Rebecca** et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/01971 A1

(54) Title: USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEAT FAILURE

(57) Abstract: The present invention relates to the use of a cortisol antagonist in the manufacture of a medicament for the treatment of heart failure as well as to a method of treating heart failure which comprises administration of a cortisol antagonist and to a product containing (a) a cortisol antagonist and (b) a second drug as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEAT FAILURE

The present invention relates to heart failure and in particular to the use of a particular class of compounds for the treatment of heart failure.

Heart failure, which is generally characterised by impaired cardiac function and exercise intolerance affects a very large number of people worldwide, particularly in the Western world. Heart failure and its complications are responsible for premature death in a proportion of sufferers and generally curtails the working life and range of activities which can be undertaken by the sufferer, as well significantly reducing overall quality of life. Heart failure is found in both sexes, young and old but is particularly prevalent in males and elderly or middle aged people.

Heart failure may be caused by a number of different underlying heart diseases. Heart diseases and events which may be a factor in causing heart failure include valvular heart disease, valvular stenosis, heart muscle disease, myocardial ischemia or infarction, cardiomyopathia and infiltrative process or inflammatory process of either the muscle, endocardium or epicardium of the heart.

As heart failure is a common and serious condition, significant efforts have been made by the medical community towards developing treatments for heart failure. A successful treatment should improve quality of life, prevent or slow progression of cardiac dysfunction and prolong life. Non-pharmacological treatments include modified diets to reduce sodium retention and cause weight loss and exercise programmes, although there is a conflict between the need to improve ventricular performance which is aided by bed rest and a desire to improve exercise intolerance and maintain conditioning which is favoured by a moderate exercise

regime. In some cases heart failure will be treated by surgical means including full heart transplantation.

A number of pharmaceuticals are available for the treatment of heart failure and for the most part these fall into three broad categories, diuretics, vasodilators and inotropic drugs. Diuretic therapy seeks to maintain intravascular volume at the lowest level compatible with optimal cardiac performance. A reduction in intravascular volume has the advantage of reducing interstitial fluid by allowing its reabsorption into the vascular space. Furosemide and/or metolazone have been used as diuretics in the treatment of heart failure but the use of these and other diuretics may lead to an undesirable drop in intracellular potassium levels. Potassium levels should be monitored and potassium supplementation may be required.

Vasodilator drugs may be useful in increasing stroke volume due to a reduction in vascular impedance and in reducing preload due to an increase in venous capacitance. Optimal treatment using vasodilators will often require coadministration of an arterial dilator such a hydralazine or minoxidil and a venodilator such as isosorbide dinitrate.

Treatment with a diuretic and/or vasodilator may be supplemented by an inotropic drug such as digoxin, dobutamine or aminone.

In addition, a patient suffering from heart failure may, in certain circumstances be prescribed antiarrhythmic drugs, β-adrenoreceptor blockers, anticoagulants, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II antagonist.

While a large number of pharmaceuticals are available to the physician for treating heart failure, different patients will have different needs and successful treatment will often require administration of a range of complementary drugs. Adverse reactions by some patients to particular drugs and drug intolerance

means there is a continuing demand for new drugs of use in the treatment of heart failure, as physicians strive to find the best drug or combination of drugs for each sufferer. Moreover, heart disease is so widespread that the public and doctors alike demand ever more effective methods of treatment which can provide a higher quality of life for longer periods.

It has now surprisingly been found that administration of a cortisol antagonist is effective in the treatment of heart failure and symptoms associated with heart failure.

Thus, in one aspect, the present invention provides the use of a cortisol antagonist for the manufacture of a medicament for the treatment of heart failure.

'Heart failure' can be defined clinically as a syndrome of ventricular dysfunction accompanied by reduced exercise capacity. Typically, there is a characteristic pattern of hemodynamic, renal and neural responses. In effect, heart failure is the inability of the heart to pump blood at an adequate rate to fulfill tissue metabolic requirements or the ability to do so only at an elevated filling pressure. Heart failure typically results in an inability to drain away body fluid which may cause ascites (body fluid in abdominal cavity), this often being observed in backward heart failure and when the liver is swollen. Within this general definition, it is intended to include the following types of heart failure and cortisol antagonists are suitable for use in treating all of these:

Acute congestive heart failure, a rapidly occurring deficiency in cardiac output marked by venocapillary congestion, hypertension and oedema, usually pulmonary oedema.

Backward heart failure, a concept of heart failure stating that imbalance of performance of the ventricles due to dysfunction of one results in a rise in pressure

behind that ventricle, with backward transmission of the increased pressure and consequent rise in venous pressure and distension.

Congestive heart failure (CHF), a clinical syndrome due to heart disease, characterised by breathlessness and abnormal sodium and water retention, often resulting in oedema. The congestion may occur in the lungs or peripheral circulation or both, depending on whether the heart failure is right-sided or general.

Diastolic heart failure, heart failure due to a defect in ventricular filling caused by an abnormality in diastolic function.

Forward heart failure, a concept of heart failure that emphasizes the inadequacy of cardiac output relative to body needs; oedema is attributed primarily to renal retention of sodium and water, and venous distention is considered a secondary feature.

High-output heart failure, heart failure in which the cardiac output remains high enough to maintain a brisk circulation with warm extremities but is inadequate to meet demand; it is most often associated with hyperthyroidism, anemia, arteriovenous fistulas, beriberi, osteitis deformans or sepsis.

Left-sided heart failure, left ventricular failure, failure of adequate output by the left ventricle despite an increase in distending pressure and in end-diastolic volume, with dyspnea, orthopnea and other signs and symptoms of pulmonary congestion and oedema.

Low-output heart failure, heart failure in which cardiac output is decreased, as in most forms of heart disease, leading to clinical manifestations of impaired peripheral circulation and peripheral vasoconstruction (cold, pale extremities, cyanosis, narrowed pulse pressure).

Right-sided heart failure, right ventricular failure, failure of proper functioning of the right ventricle, with venous engorgement, hepatic enlargement,

and subcutaneous oedema; it is often combined with left-sided heart failure.

Systolic heart failure, heart failure due to a defect in expulsion of blood caused by an abnormality in systolic function.

A cortisol antagonist is particularly well suited to the treatment of congestive, diastolic, backward, low-output and right-sided heart failure. Thus, the treatment of these conditions represents a preferred aspect of the present invention.

According to the New York Functional Classifications (Ganiats, T.G., Browner, D.K., Dittrich, H.C. in American Heart Journal (1998) 135: 5 Pt 1, 819-824) the severity of heart failure can be divided into four classes as follows:

Class I - no limitation of physical activity: ordinary physical activity does not cause undue fatigue, shortness of breath or palpitation;

Class II - slight limitation of physical activity; such patients are comfortable at rest, ordinary physical activity results in fatigue, shortness of breath, palpitations or angina;

Class III - marked limitation of physical activity; although patients are comfortable at rest, less than ordinary activity will lead to symptoms;

Class IV - inability to carry out any physical activity without discomfort: symptoms of congestive heart failure are present even at rest. With any physical activity increased discomfort is experienced.

Cortisol antagonists are suitable for the treatment of all classes of heart failure, particularly classes II to IV.

By 'cortisol antagonist' is meant any compound or agent which reduces production of cortisol or circulating levels of biologically active cortisol or which limits the biological effects of cortisol by inhibiting cortisol (glucocorticoid) receptors

competitively or non-competitively, or in any other way. The term includes agents which interfere with the regulation of cortisol synthesis along the so-called hypothalmic-pituitary-adrenal gland (HRA) axis. Thus a "cortisol antagonist" may broadly be regarded as any compound or agent which antagonises or inhibits (i.e. reduces or prevents) cortisol activity.

A large number of agents are known to suppress glucocorticoid production or inhibit their receptor binding in humans: sodium valporate (Aggernaes, H. et al. Acta Psychïatr. Scand. (1988) 77 170-174); Enkephalins and their synthetic analogues (Stubbs, W.A. et al. The Lancet (1978) 1225-1227); Opioids such as loperamide, commercially available under the trademark IMODIUM from Janssen Pharmaceutica N.V.; the antihypertensive drug Clonidine (Slowinska-Srzednicka, J. et al. European Journal of Clinical Pharmacology (1988) 35 115-121); Oxytocin (Legros, J.J. et al. Endocrinologica (1987) 114 345-349) and Mifepristone, known as RU 486 or RU 38486 available from Roussel-Uclaf. Mifepristone and other antagonists which operate at the receptor level are a class of preferred active agents for use in the present invention.

Any of the above agents or any of the large number of cortisol synthesis inhibitors known in the art, e.g. econazole (Squibb, U.K.), ketoconazole and miconazole (Janssen, Belgium) and their derivatives, may be used as cortisol antagonists according to the present invention. In the case of econazole and miconazole, derivatives of these particular compounds are preferred.

'Derivatives' encompass compounds which are structurally related to the primary compound (e.g. ketoconazole) but are functionally equivalent or superior. Thus, a derivative might have a slightly inferior therapeutic activity but be a useful molecule because it exhibits reduced toxicity, is more convenient to formulate or administer etc. Derivatives may include

salts or other variants which have been more significantly modified while retaining functionally important structural motifs in common with the primary compound. In the case of econazole and miconazole, such derivatives may exhibit better overall properties than the primary compounds in terms of therapeutic activity and toxicity, for example.

Preferred cortisol antagonists include those compounds which inhibit the synthesis of cortisol, either by reducing the production of cortisol in any form or which cause the production of a modified form of cortisol which is less biologically active than native, naturally occurring cortisol. Preferably, cortisol synthesis inhibitors will act on the cortisol synthetic pathway in a way which does not significantly affect the normal production of the other steroid hormones, in particular which does not significantly effect production of mineralocorticoids such as aldosterone. The 'significance' of the effect is considered in terms of the biological, *in vivo*, effect. Ketoconazole and its derivatives are preferred for use according to the invention and in addition, isomers of ketoconazole are known and may be used, individually or in combination (Rotstein et al., J. Med. Chem. (1992) 35, 2818-2825). The Cis-2S,4R and Cis-2R,4S isomers are particularly preferred for use in accordance with the present invention. These isomers may be used individually or in combination as in the commercially available product Fungoral™ (Janssen-Cilag, Belgium).

In the case of cortisol antagonists which act via cortisol (glucocorticoid) receptors, the antagonist will preferably have an effect on the receptors in the kidney and/or the heart. The binding affinity which an antagonist has for receptors in different organs may not be uniform and preferably the antagonist used in the present invention will have a comparatively higher binding affinity for the glucocorticoid receptors in the

heart and/or kidney.

The cortisol antagonists for use according to the present invention have a sufficiently negative effect on circulating levels of biologically active cortisol or on its biological efficacy to cause a measurable and significant improvement in heart failure or its associated symptoms. It is not expected that in all cases treatment will be totally successful but "treatment" according to the present invention should include improvement in one or more of the following areas: fluid retention including oedema of lower limbs and fluid in the lungs (pulmonary oedema), dyspnea, liver enlargement, heart rate, stroke volume, shortness of breath, exercise intolerance and general physical and mental health. Particularly, improvements are seen in symptoms associated with fluid retention (e.g. liver enlargement, peripheral and pulmonary odema and ascites).

Advantageously, according to the uses and method of the present invention, one or more of the following benefits may be achieved:

a 10% or more reduction in liver size,

a 10% or more reduction in heart rate,

a 15% or more improvement in physical health according to the test described in the Examples herein.

Further symptoms which often occur with heart failure, whatever the cause, are enlargement of the heart and development of a fibrosis in the heart muscle. These morphological aspects of heart failure can also be treated successfully by administration of a cortisol antagonist.

Heart failure will be diagnosed when a patient has impaired cardiac function and exercise intolerance. All patients with heart failure, whether newly diagnosed or at a more advanced stage can be considered for treatment in accordance with the present invention. Treatment with a cortisol antagonist may be successful whatever

the underlying disease which has resulted in a diagnosis of heart failure. The observations which have resulted in the present invention relate to the treatment of heart failure itself and its symptoms not to the diseases and risk factors which may give rise to heart failure. Various medical conditions such as cardiovascular disease may or may not lead to heart failure but as the implications for untreated heart failure are serious, it is beneficial to have available treatments specifically for heart failure and its associated symptoms.

Thus, in a further aspect is provided a method of treating heart failure in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

Alternatively viewed, according to the method of the invention, an amount of cortisol antagonist is administered which is effective to improve one or more of the symptoms of heart failure; these areas in which improvement may be observed are discussed above.

A 'pharmaceutically effective' amount can be determined with reference to the various areas discussed herein in which treatment may provide measurable improvements, and selected with reference to the Examples and standard practices for deciding dosage amounts.

Generally, patients in need of such a treatment will be diagnosed as suffering from heart failure by reference to the clinical definitions provided herein or other medically accepted criteria.

The cortisol antagonist or antagonists may be administered to the patient in any convenient form, orally or by intravenous, enteral or parenteral routes. Preferably the cortisol antagonist will be administered by oral routes.

Alternatively viewed, the invention provides a method of improving cardiac function and reducing

exercise intolerance in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

Likewise, the invention provides the use of a cortisol antagonist in the production of a medicament for improving cardiac function and reducing exercise intolerance.

An improvement in cardiac function may include a reduction in heart rate and/or an increase in stroke volume. Exercise intolerance is generally characterised by breathlessness and other signs of fatigue, cramp etc., primarily due to an inability of the patient suffering from heart failure to supply sufficient oxygenated blood to muscle and other organs and tissue. It can be measured by a subnormal physical exercise test (Faggiano, P., D'Aloia, A., Gualeni, A. and Giordano, A. American Journal of Cardiology (1998) 15 81:4, 437-42).

Compositions comprising a cortisol antagonist as defined above are preferably formulated prior to administration.

The present invention therefore also provides a pharmaceutical composition for use in the treatment of heart failure, said composition comprising a cortisol antagonist together with at least one pharmaceutically acceptable carrier, diluent or excipient. The active ingredient in such compositions may comprise from 0.05% to 99% by weight of the formulation, more preferably 0.1% to 1.0%.

By "pharmaceutically acceptable" is meant that the ingredients must be compatible with other ingredients of the composition as well as physiologically acceptable to the recipient.

The pharmaceutical compositions may be formulated according to any of the conventional methods known in the art and widely described in the literature. Thus, the active ingredient may be incorporated, optionally together with other active substances, with one or more

conventional carriers, diluents and/or excipients, to produce conventional galenic preparations such as tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions sterile packaged powders, and the like.

Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, aglinates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, water, water/ethanol, water/ glycol, water/polyethylene, glycol, propylene glycol, methyl cellulose, methylhydroxybenzoates, propyl hydroxybenzoates, talc, magnesium stearate, mineral oil or fatty substances such as hard fat or suitable mixtures thereof. The compositions may additionally include lubricating agents, wetting agents, emulsifying agents, suspending agents, preserving agents, sweetening agents, flavouring agents, and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. Sustained and/or delayed release formulations may be particularly convenient.

The active agents are preferably formulated into tablets, each tablet containing a predetermined amount of active ingredient.

Suitable doses will vary from patient to patient and can be determined by the physician in accordance with the weight, age and sex of the patient and the severity of the condition and also the particular antagonist selected. A typical total daily dose will be in the region of 50 or 100-1200 mg of a cortisol

antagonist which may be administered as a single dose or in several smaller doses during the day. Typical single doses will be in the region of 100-800 mg. Administration may advantageously be at around 10.00 p.m. in order to reduce cortisol activity during the night when natural cortisol levels are at their highest. Ketoconazole is preferably administered as a daily dose of 200-1000 mg, e.g. 300-600 mg.

During the majority of the treatment period, typically 75% or more, effective treatment will be daily. By 'effective treatment' is meant that the circulating levels of the cortisol antagonist are at physiologically effective levels; this may be achieved by daily administration or, for example, by use of a controlled-released formulation which offers sustained release over several days or more.

Improvements in patients treated in accordance with the present invention may be seen immediately or after some (e.g. 2-4) weeks and treatment should normally be continued for 3 months or more to achieve maximum benefits. As with most treatments for heart failure, it may be necessary to administer the cortisol antagonist for the rest of the patient's life. Such long term treatment may not necessarily be continuous and the optimum dose may vary during the course of treatment.

Use of a cortisol antagonist may be in place of or in addition to use of other drugs for the treatment of heart failure. This may improve the efficacy of the overall treatment regime and/or reduce the amount of drugs required by the patient or enable the physician to cease administration of a drug which is causing undesirable side effects.

As well as treatments which comprise the co-administration of a cortisol antagonist and one or more other drugs for the treatment of heart failure, medicaments and treatments in accordance with the present invention may comprise more than one cortisol

antagonist. Treatment may involve administration of an antagonist which affects synthesis of cortisol in the adrenal glands and also treatment with an antagonist which inhibits the activity of cortisol at the receptor level. Furthermore treatment may involve administration of an antagonist which operates along the HPA axis as mentioned above.

Thus, in a further aspect the present invention provides a product containing (a) a cortisol antagonist and (b) a second drug (e.g. a second agent effective in the treatment of heart failure) as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

Suitable 'second drugs or agents' include known drugs for use in the treatment of heart failure as are discussed above e.g. diuretics, vasodilators, inotropic drugs, ACE inhibitors and angiotensin II antagonists and also a second cortisol antagonist as defined herein.

Where two or more active agents are administered, they may be given simultaneously to the patient or times of administration may be staggered throughout the day or treatment cycle.

The invention will be further described with reference to the following non-limiting Examples.

Example 1

Subject 1: A 44 year old man exhibiting the symptoms of heart failure, including retention of body fluid manifested as moderate oedema of lower limbs and body fluid in the lungs. Also, moderate dyspnea and increased heart rate as well as an increase in liver size (indicative of fluid retention in the liver). Patient being treated for heart failure with lisinopril (Zestril®)

Treatment: 400 mg of a racemate of the Cis-2S,4R and Cis-2R,4S isomers of ketoconazole (Fungoral™ tablets - Janssen-Cilag, Belgium) was administered at 10.00 pm every day for a 3 month period.

Observations: Body weight reduced by 3.8 kg - attributable to a reduction in fluid retention.

Heart rate fell from 72 beats/min to 62 beats/min.

Reduction in liver size of 10% and a resulting reduction in liver transaminases
S-ASAT reduced from 0.44 to 0.30 μKat/L
S-ALAT reduced from 1.0 to 0.39 μKat/L

Dyspnea, oedema of lower limbs and body fluid in the lungs reduced.

Physical health as measured by a subnormal physical exercise test (Faggiano, P. et al. supra) improved by 15%.

Dose of lisinopril (Zestril®) could be reduced to half of original dose

Example 2

Subject 2: A 63 year old woman exhibiting the same symptoms of heart failure as subject 1. Patient being treated for heart failure with furosemid (40 mg/ day)

Treatment: As for Example 1.

Observations: Body weight reduced by 4.2 kg.

Heart rate fell from 74 beats/min to 60 beats/min.

Reduction in liver size of 15% and in liver transaminases.
S-ASAT reduced from 0.58 to 0.32 μKat/L
S-ALAT reduced from 0.92 to 0.68 μKat/L

Dyspnea, oedema of lower limbs and body fluid in lungs reduced.

Physical health, as measured by a subnormal physical exercise test, improved by 20%.

Dose of furosemid could be stopped within 6 weeks of commencement of treatment with ketoconazole.

Claims

1. Use of a cortisol antagonist in the manufacture of a medicament for the treatment of heart failure.

2. A use as claimed in claim 1 wherein the heart failure is categorised as congestive, diastolic, low-output or right-sided heart failure.

3. A use as claimed in claim 1 or claim 2 wherein the cortisol antagonist is an inhibitor of cortisol synthesis.

4. A use as claimed in claim 3 wherein the inhibitor of cortisol synthesis is ketoconazole or a derivative thereof.

5. A use as claimed in claim 4 wherein the cortisol synthesis inhibitor is the Cis-2S,4R and/or the Cis-2R,4S isomer of ketoconazole.

6. A use as claimed in any of the preceding claims wherein the medicament is for use in the treatment of enlargement of the heart or a fibrosis in the heart muscle.

7. Use of a cortisol antagonist in the manufacture of a medicament for the treatment of one or more symptoms associated with heart failure selected from the group comprising, oedema of lower limbs, pulmonary oedema, dyspnea, liver enlargement, increased heart rate, reduced stroke volume, shortness of breath and exercise intolerance.

8. A use as claimed in claim 7 wherein the medicament is for use in the treatment of pulmonary oedema.

9. A use as claimed in any one of the preceding claims wherein the daily dose of the cortisol antagonist to a patient being treated is 100-1200 mg.

10. A method of treating heart failure in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

11. A method of treating one or more symptoms associated with heart failure selected from the group comprising, oedema of lower limbs, pulmonary oedema, dyspnea, liver enlargement, increased heart rate, reduced stroke volume, shortness of breath and exercise intolerance in a mammal which method comprises administering a pharmaceutically effective amount of a cortisol antagonist to said mammal.

12. A product containing (a) a cortisol antagonist and (b) a second drug as a combined preparation for simultaneous, separate or sequential use in the treatment of heart failure or in improving cardiac function and reducing exercise intolerance.

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PATENT COOPERATION TREATY

PCT

REC'D 09 OCT 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9.32.69402/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02551	03/07/2000	02/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant CORTENDO AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/02/2001	04.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02551

I. Basis of th r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11 in respect of industrial applicability.

because:

☒ the said international application, or the said claims Nos. in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3, 6-10 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 8-9, 12
	No:	Claims	1-2, 6-7, 10-11
Inventive step (IS)	Yes:	Claims	8-9
	No:	Claims	1-7, 10-12
Industrial applicability (IA)	Yes:	Claims	1-10, 12

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R Item I

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Claims 1-3 and 6-10 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefor are the following:
Claims 1-3 and 6-10 refer to the use of cortisol antagonists for treating heart failure. No further technical characteristics are given for the cortisol antagonists. Consequently, the an opinion will be formulated for those parts of the application which have actually been searched, namely the use of the cortisol antagonists explicitly disclosed at page 6, lines 8-30 in the description, as well as the compounds of claims 4-5.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
Reference is made to the following documents:
D1: US-A-4603141
D2: Derwent abstract, AN: 90080584 (& Kardiologiia, Sep. 1989, 29(9), 81-3)

1. Document D1 discloses (see the whole document) the use of clonidine for treating congestive heart failure and increase the exercise tolerance of such an individual. Clonidine is expicitly mentioned in the application at page 6 as one of the cortisole antagonists for use in the present invention. The subject matter of claims 1-2, 6-7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

2. Document D2 discloses (see abstract) that synthetic opioids, such as synthetic enkephalins, possess cardioprotective effects and can be used to reverse stress-induced damage of the myocardium. Enkephalins are amongst the substances

disclosed for use in the present invention. The subject matter of claims 1-2, 7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

3. An objection of lack of inventive step (Art. 33(3) PCT) is also raised against the subject matter of claims 3-5 of the present application for the following reasons. Document D1, which is considered to represent the closest prior art, discloses the use of clonidine, an antihypertensive known to act as cortisol antagonist, for the treatment of congestive heart failure. The subject matter of calims 3-5 differs from that of D1 in that an inhibitor of cortisol synthesis, namely ketoconazole, is used instead. Substitution of a known cortisol antagonist for another known one for treating the same disease, in this case heart failure, can only be considered as inventive if it leads to unexpected results.

4. The above inventive step objection (Art. 33(3) PCT) applies also to the subject matter of claim 12 which relates to combination compositions of a cortisol antagonist and a second drug for treating heart failure. As in above such combination can only be considered as inventive if it leads to unexpected results.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0018424	06.04.00	27.09.99	25.09.98

Document WO-A-0018424 discloses (see claims 1, 4-8) pharmaceutical compositions containing substances having oxytocin activity for improving cell regeneration after a heart attack, and is therefore prejudicial to the novelty of claims 1-2, 7 and 10-11 of the present application. Nevertheless, the validity of filng and priority dates has not been checked.

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0024402	04.05.00	27.10.98	

Document WO-A-0024402 discloses (see claims 1, 2, 5, 8-9) pharmaceutical

compositions containing antifungal agents, ketoconazole being explicitly mentioned, for treating tissue scleroses in mammals. Tissue scleroses resulting from myocardial infarction are explicitly mentioned. Document WO-A-0024402 is therefore prejudicial for the novelty of claims 1-4, 7, 9-11 of the present application.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII

Certain observations on the international application

In claim 12 the term "second drug" is unclear. It should be defined according to the description, page 13, lines 10-11 as "second drug effective in the treatment of heart failure".

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GARDNER, Rebecca
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 04.10.2001
Applicant's or agent's file reference 9.32.69402/001	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02551	03/07/2000	02/07/1999

Applicant
CORTENDO AB

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Geier, A Tel.+49 30 25901-706

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9.32.69402/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02551	03/07/2000	02/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant CORTENDO AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/02/2001	04.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02551

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-15 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11 in respect of industrial applicability.

because:

☒ the said international application, or the said claims Nos. in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3, 6-10 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 8-9, 12
	No:	Claims	1-2, 6-7, 10-11
Inventive step (IS)	Yes:	Claims	8-9
	No:	Claims	1-7, 10-12
Industrial applicability (IA)	Yes:	Claims	1-10, 12

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Claims 1-3 and 6-10 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefor are the following:
Claims 1-3 and 6-10 refer to the use of cortisol antagonists for treating heart failure. No further technical characteristics are given for the cortisol antagonists. Consequently, the an opinion will be formulated for those parts of the application which have actually been searched, namely the use of the cortisol antagonists explicitly disclosed at page 6, lines 8-30 in the description, as well as the compounds of claims 4-5.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
Reference is made to the following documents:
D1: US-A-4603141
D2: Derwent abstract, AN: 90080584 (& Kardiologiia, Sep. 1989, 29(9), 81-3)

1. Document D1 discloses (see the whole document) the use of clonidine for treating congestive heart failure and increase the exercise tolerance of such an individual. Clonidine is expicitly mentioned in the application at page 6 as one of the cortisole antagonists for use in the present invention. The subject matter of claims 1-2, 6-7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

2. Document D2 discloses (see abstract) that synthetic opioids, such as synthetic enkephalins, possess cardioprotective effects and can be used to reverse stress-induced damage of the myocardium. Enkephalins are amongst the substances

disclosed for use in the present invention. The subject matter of claims 1-2, 7 and 10-11 does not meet the requirements of Art. 33(2) and 33(3) PCT.

3. An objection of lack of inventive step (Art. 33(3) PCT) is also raised against the subject matter of claims 3-5 of the present application for the following reasons. Document D1, which is considered to represent the closest prior art, discloses the use of clonidine, an antihypertensive known to act as cortisol antagonist, for the treatment of congestive heart failure. The subject matter of calims 3-5 differs from that of D1 in that an inhibitor of cortisol synthesis, namely ketoconazole, is used instead. Substitution of a known cortisol antagonist for another known one for treating the same disease, in this case heart failure, can only be considered as inventive if it leads to unexpected results.

4. The above inventive step objection (Art. 33(3) PCT) applies also to the subject matter of claim 12 which relates to combination compositions of a cortisol antagonist and a second drug for treating heart failure. As in above such combination can only be considered as inventive if it leads to unexpected results.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0018424	06.04.00	27.09.99	25.09.98

Document WO-A-0018424 discloses (see claims 1, 4-8) pharmaceutical compositions containing substances having oxytocin activity for improving cell regeneration after a heart attack, and is therefore prejudicial to the novelty of claims 1-2, 7 and 10-11 of the present application. Nevertheless, the validity of filng and priority dates has not been checked.

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-0024402	04.05.00	27.10.98	

Document WO-A-0024402 discloses (see claims 1, 2, 5, 8-9) pharmaceutical

compositions containing antifungal agents, ketoconazole being explicitly mentioned, for treating tissue scleroses in mammals. Tissue scleroses resulting from myocardial infarction are explicitly mentioned. Document WO-A-0024402 is therefore prejudicial for the novelty of claims 1-4, 7, 9-11 of the present application.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII

Certain observations on the international application

In claim 12 the term "second drug" is unclear. It should be defined according to the description, page 13, lines 10-11 as "second drug effective in the treatment of heart failure".

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
9.69402/001		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02551	03/07/2000	02/07/1999
Applicant		
CORTENDO AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF CORTISOL ANTAGONISTS IN THE TREATMENT FOR HEAT FAILURE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3 and 6-10 refer to the use of cortisol antagonists for treating heart failure. No technical characteristics are given for the antagonists.
In consequence the scope of calims 1-10 is ambiguous and vague, and their subject matter is neither sufficiently disclosed nor supported (Art. 5 and 6 PCT). The serch has been performed for the parts of teh application which are sufficiently disclosed and supported, namely the cortisol antagonists listed in the description in page 6, lines 8-30.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02551

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61P9/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 18424 A (ENTRETECH MEDICAL AB) 6 April 2000 (2000-04-06) claims 1,4-8	1,2,7, 10,11
P,X	WO 00 24402 A (R. ANTONOV) 4 May 2000 (2000-05-04) claims 1,2,5,8,9	1-12
X	US 4 603 141 A (THOMAS D. GILES) 29 July 1986 (1986-07-29) the whole document	1,2,7, 10,11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2000	07/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; AN: 90080584, XP002150683 & Kardiologiia, (1989 Sep), 29(9), 81-3 (& G. F. Dvortsin) abstract	1,2,7, 10,11
A	D. A. SCHEUER ET AL: "Chronic cortisone treatment increases myocardial infarct size in rats with ischemia-reperfusion injury" AMERICAN JOURNAL OF PHYSIOLOGY, vol. 272, no. 6(2), June 1997 (1997-06), pages R2017-R2024, XP000951448 abstract	1-12
A	LOOSE D S ET AL: "Ketoconazole Binds to Glucocorticoid Receptors and Exhibits Glucocorticoid Antagonist Activity in Cultured Cells" JOURNAL OF CLINICAL INVESTIGATION,US,NEW YORK, NY, vol. 72, 1 July 1983 (1983-07-01), pages 404-408, XP002095830 ISSN: 0021-9738 abstract	1-12
A	SPITZ I M ET AL: "MIFEPRISTONE (RU 486) - A MODULATOR OF PROGESTIN AND GLUCOCORTICOIDACTION" NEW ENGLAND JOURNAL OF MEDICINE, THE,US,MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, 1993, pages 404-412, XP000909997 ISSN: 0028-4793 page 408, right-hand column, last paragraph -page 409, left-hand column page 409, right-hand column, line 41 - line 48	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0018424 A	06-04-2000	AU 6493199 A	17-04-2000
WO 0024402 A	04-05-2000	AU 1036999 A	15-05-2000
		AU 6347199 A	15-05-2000
		WO 0024403 A	04-05-2000
US 4603141 A	29-07-1986	NONE	